Communication

1,2-Amino Alcohols via Cr/Photoredox Dual Catalyzed Addition of #-Amino Carbanion Equivalents to Carbonyls

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1,2-Amino Alcohols *via* Cr/Photoredox Dual Catalyzed Addition of α-Amino Carbanion Equivalents to Carbonyls

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ABSTRACT: Herein, we report the synthesis of protected 1,2-amino alcohols starting from carbonyl compounds (mostly aldehydes) and α-silyl amines. The reaction is enabled by a Cr/photoredox dual catalytic system that allows the *in situ* generation of α-amino carbanion equivalents which act as nucleophiles. The unique nature of this reaction was demonstrated through the aminoalkylation of ketones and an acyl silane, classes of electrophiles that were previously unreactive towards addition of alkyl–Cr reagents. Overall this reaction broadens the scope of Cr-mediated carbonyl alkylations and discloses an underexplored retrosynthetic strategy for the synthesis of 1,2-amino alcohols.

The 1,2-amino alcohol unit is an important motif in various natural products, medicinally active compounds and privileged ligands. More than 300,000 compounds containing this unit are known, including >2,000 natural products, >80 FDA approved drugs and >100 drug candidates.[1] The formation of these structures has therefore received widespread attention from the synthetic organic chemistry community.[2] Classically, 1,2-amino alcohols are prepared *via* nucleophilic ring-opening of epoxides with amines.[3] Epoxides are nevertheless highly reactive and often difficult to prepare, resulting in drawbacks concerning selectivity and (late-stage) applicability of this approach. Alternatively, a retrosynthetic cut of the connecting C(sp^3)–C(sp^3) bond can also be envisaged, making use of a cornerstone of organic synthesis, the addition of carbanion equivalents to carbonyls.[4] This approach is still underexplored, since it involves α-amino carbanions that are challenging to access because of the destabilizing interaction between the N lone pair and the carbanion.[5,6] The most general protocol to form these species relies on the transmetalation of the corresponding Sn compounds with Li organyls.[5c] This approach, however, has major disadvantages concerning the toxicity of the Sn-containing starting materials and byproducts, atom-economy and functional group tolerance due to the high reactivity of the Li organyls.

Compared to their Li analogs, Cr organyls have distinct advantages as nucleophiles in carbonyl functionalization. Most importantly, Cr-mediated additions have an unparalleled functional group tolerance in both reaction partners.[7] In line with this, these reactions are highly chemoselective for aldehydes and tolerate other electrophilic functional groups such as ketones, esters or nitriles. It is therefore no surprise that the addition of *in situ* formed Cr organyls to carbonyls emerged as a valuable tool in total syntheses[8], which is now known as the Nozaki-Hiyama-Kishi (NHK) reaction.[9] Although various Cr organyls can be formed using classical NHK conditions, i.e. the Ni catalyzed reductive metalation of organic halides with Cr^{II} species, alkyl–Cr reagents have remained an exception. This inspired Takai[10a] and recently Shenvi[10b] and Baran[10c] to develop elegant methods for accessing alkyl–Cr reagents that allowed the chemoselective alkylation of aldehydes with alkyl halides,

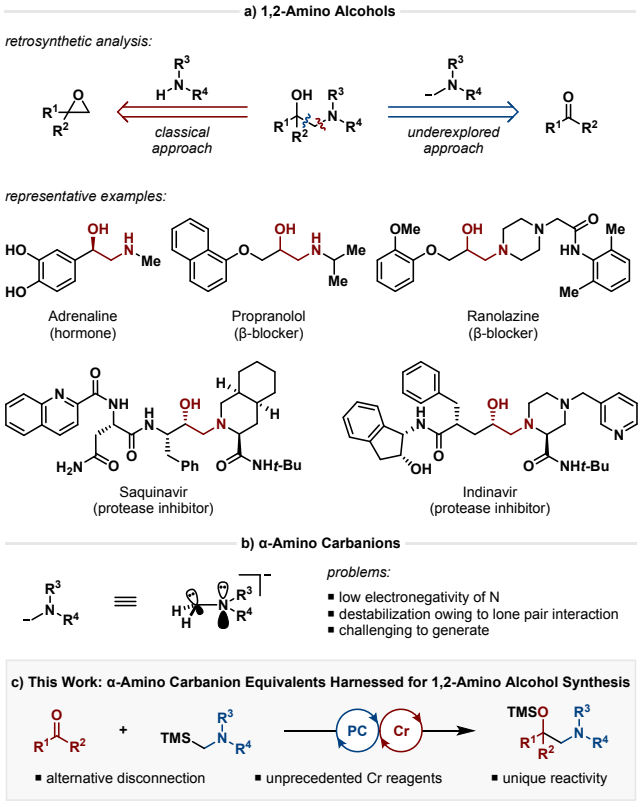


Figure 1. (a) 1,2-Amino alcohols: Retrosynthetic analysis and representative examples. (b) α-Amino carbanions as underexplored intermediates. (c) This work: Silyl aminoalkylation of carbonyls for the synthesis of protected 1,2-amino alcohols.

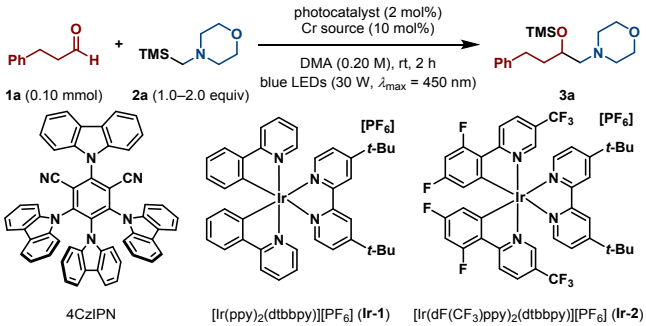
alkenes or activated carboxylic acids, respectively. The key to success was a Cr/Co dual catalytic system in Takai's and Shenvi's protocols, while Baran's protocol makes use of standard NHK conditions to generate the alkyl–Cr compounds. Although these protocols expanded the scope of Cr-mediated carbonyl functionalizations significantly, the need for (super-)stoichiometric quantities of Cr salts is a drawback. Importantly, α-aminoalkyl–Cr species cannot be accessed using either of these protocols.[11a]

With this in mind, we sought to develop a catalytic protocol to generate α-aminoalkyl–Cr reagents[11b], thereby establishing a simple and mild alternative to the nucleophilic ring-opening of epoxides to access 1,2-amino alcohols. Recently, our group[12a] and Kanai [12b] independently developed Cr/photoredox[13] dual catalytic systems that enabled allylations of aldehydes, similar to the NHK reaction. We expected that these dual catalytic systems would be perfectly suited for the generation of α-aminoalkyl–Cr species. We initially chose to use α-silyl amines as the α-aminoalkyl–Cr precursor for our studies, since these do not exhibit regioselectivity issues in the radical generation step and are readily prepared in a single step.[14]

To test our proposal, we reacted aldehyde **1a** (1.0 equiv) with α-silyl amine **2a** (2.0 equiv) in the presence of catalytic amounts of the organic dye 4CzIPN and $CrCl_2$ under visible light-mediated photocatalytic conditions. Pleasingly, after only 2 h reaction time, we obtained the silyl-protected 1,2-amino alcohol product **3a** in various polar-aprotic solvents (81% yield in DMA, Table 1, Entry 1, for further details, see the Supporting Information). Ir-based photocatalysts such as $[Ir(ppy)_2(dtbbpy)][PF_6]$ (**Ir-1**) and $[Ir(dF(CF_3)ppy)_2(dtbbpy)][PF_6]$ (**Ir-2**) performed slightly better and improved the yield to 91% (Table 1, Entries 2,3). Bench-stable $CrCl_3$ could also be employed as the catalyst instead of air-sensitive $CrCl_2$, which greatly improves the practicality of our protocol (99% yield, Table 1, Entry 4). The reaction can also be conducted using equimolar quantities of the starting materials (Table 1, Entry 5), although we consistently observed higher yields when the α-silyl amine was used in excess. Control experiments verified that the photocatalyst, $CrCl_3$ and light are essential for the reaction and no product was formed in absence of any one of these (Table 1, Entries 6–8). Noteworthy, this reaction proceeds catalytically, with perfect atom-economy[15] and without the need for additives. Furthermore, we investigated the sensitivity of our 1,2-amino alcohol synthesis towards operational variations in reaction conditions in order to improve the reproducibility (Figure 2).[16] The reaction is highly sensitive to moisture, but other parameters (light intensity, temperature, concentration, scale) only have a minor influence on the reaction yield.

Having established optimal reaction conditions, we then turned our attention towards the substrate scope of this aminoalkylation protocol (Table 2). First, we explored the scope regarding the amine moiety. Apart from morpholine (**3a**), other important N-heterocycles[17] such as thiomorpholine (**3b**), piperidine (**3c**) and various piperazines (**3d–3f**) were well tolerated. In all cases the

Table 1. Optimization of the 1,2-amino alcohol synthesis.



Entry	Photocatalyst	Cr source	1a/2a	Yield
1	4CzIPN	$CrCl_2$	1.0/2.0	81%
2	**Ir-1**	$CrCl_2$	1.0/2.0	86%
3	**Ir-2**	$CrCl_2$	1.0/2.0	91%
4	**Ir-2**	$CrCl_3$	1.0/2.0	99%
5	**Ir-2**	$CrCl_3$	1.0/1.0	95%
6	–	$CrCl_3$	1.0/2.0	0%
7	**Ir-2**	–	1.0/2.0	0%
8[a]	**Ir-2**	$CrCl_3$	1.0/2.0	0%

Performed on 0.10 mmol scale. Yields were determined by GC-FID analysis using mesitylene as internal standard. [a]In the absence of light. DMA = dimethylacetamide. Ph = phenyl. rt = room temperature. TMS = trimethylsilyl. *t*-Bu = *tert*-butyl.

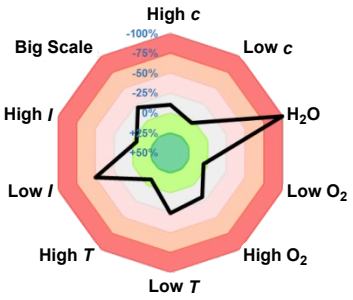
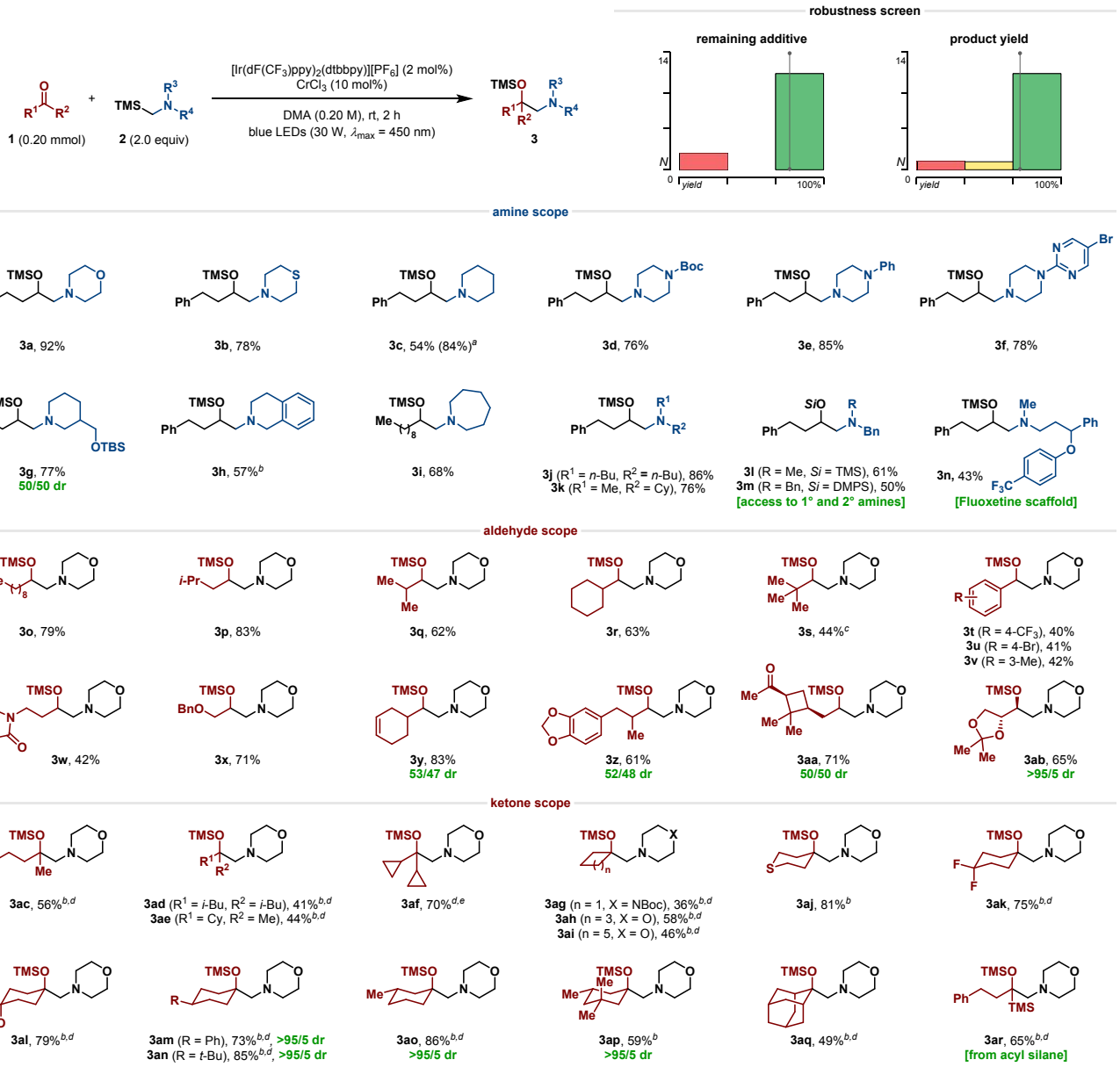


Figure 2. Sensitivity assessment of the 1,2-amino alcohol synthesis. *c* = concentration. *T* = temperature. *I* = light intensity.

products were obtained in good to excellent yields, although we observed partial decomposition of product **3c** during isolation (54% isolated yield, 84% NMR yield). Notably, other amine moieties or Lewis-basic heteroarenes, both common motifs in natural products and drugs,[17] did not affect the outcome of the reaction. Substituted piperidines (**3g, 3h**) as well as other ring sizes (**3i**) could also be employed without any erosion in yield. The reaction was also suitable for functionalization of acyclic amines (**3j–3l**) with different steric properties, including benzyl substituents (**3l, 3m**) that can be easily removed from the products (see the Supporting Information for details, product **S6** and **S7**) and thus allow the generation of primary and secondary

Table 2. Scope of the 1,2-amino alcohol synthesis *via* Cr/photoredox dual catalysis.



Standard reaction conditions: **1** (0.20 mmol, 1.0 equiv), **2** (2.0 equiv), $[Ir(dF(CF_3)ppy)_2(dtbbpy)][PF_6]$ (2.0 mol%), $CrCl_3$ (10 mol%), DMA (0.20 M), rt, 2 h. Diastereomeric ratios were determined by GC-MS analysis of the crude reaction mixture. See the Supporting Information for full experimental details. [a]NMR yield using CH_2Br_2 as an internal standard. [b]16 h reaction time. [c]5 h reaction time. [d]**2** (3.0 equiv). [e]40 h reaction time. Boc = *tert*-butyloxycarbonyl. Bn = benzyl. Cy = cyclohexyl. DMA = dimethylacetamide. DMPS = dimethylphenylsilyl. *i*-Bu = *iso*-butyl. *i*-Pr = *iso*-propyl. Me = methyl. *n*-Bu = *n*-butyl. Ph = phenyl, rt = room temperature. TBS = *tert*-butyldimethylsilyl. TMS = trimethylsilyl. *t*-Bu = *tert*-butyl.

amines as well as subsequent functionalization of the amine moiety. Furthermore, a complex Fluoxetine (Prozac®) derivative (**3n**) was observed to be reactive under the conditions, showing potential application of this methodology in late-stage functionalizations. One limitation of this method is currently the use of secondary α-aminoalkyl–Cr reagents. For these substrates we did not observe any product formation, consistent with previous reports of Takai and Baran, in which secondary alkyl–Cr species did not show reactivity towards carbonyl addition.[10a,10c]

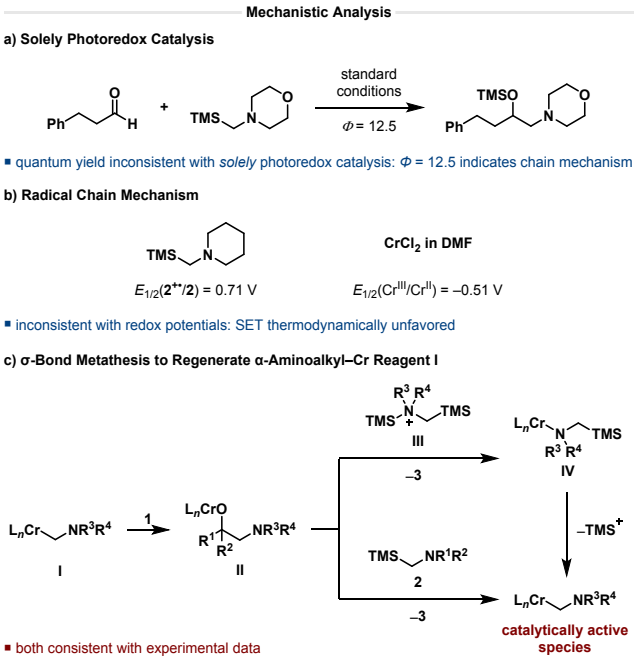


Figure 3. Mechanistic studies. (a) Determination of the reaction quantum yield. (b) Comparison of redox potentials to exclude a radical-chain mechanism. (c) Proposed σ-bond metathesis pathway. DMF = dimethylformamide. Ph = phenyl. SET = single electron transfer. TMS = trimethylsilyl.

sluggish substrates, underlining the unique nature of our reaction.[18] For aromatic aldehydes, diminished yields were observed compared to aliphatic substrates (**3t–3v**) and the pinacol coupling product was obtained as the major byproduct, presumely caused by radical-radical coupling after reduction by the photocatalyst.[19] Pleasingly, the reaction also tolerated a variety of functional groups, which all provide a handle for subsequent functionalization. Protected (**3d, 3w**) and tertiary amines (**3e, 3f**), (thio-)ethers (**3a, 3b, 3m, 3x**), alkenes (**3y**), acetals (**3z, 3ab**) and (hetero-)aryl halides (**3f, 3u**) can all be employed under this protocol. As expected for alkyl–Cr intermediates, this reaction is chemoselective for aldehyde functionalization.[7–9] In the presence of a ketone moiety, we exclusively observed functionalization at the aldehyde group and no difunctionalization (**3aa**). Interestingly, when a glyerinaldehyde derivative was employed in the reaction, the *anti*-product **3ab** was obtained selectively, consistent with a Felkin-Anh-addition of the α-aminoalkyl–Cr species to the aldehyde.[20]

To our great surprise, our protocol could also be used for the alkylation of ketones. This is especially noteworthy, as it was previously shown that alkyl–Cr^{III} species do not react with carbonyl electrophiles other than aldehydes, further distinguishing our catalytic system from classical Cr-mediated approaches.[21] Acyclic (**3ac–3af**) and cyclic (**3ag–3ar**) ketones containing functional groups such as thioethers (**3ah**), difluoromethylene groups (**3ai**) or spirocyclic acetals (**3aj**) were all compatible with this reaction. Additionally, for unsymmetrical cyclohexanones we observed selective formation of one diastereomer (**3am–3ap**), independent of the position of the substituent. Steric hindrance did not affect the outcome of the reaction (**3ap**) and also in this case, the product was obtained as a single diastereomer. Astonished about the high reactivity of our catalytic system, we evaluated other electrophiles in this aminoalkylation. Acyl silanes[22] were also observed to be reactive under the optimized conditions and yielded the 1,2-amino alcohol **3ar** in 65% yield. **3ar** contains the synthon of a Brook rearrangement and thus enables further elaboration of the product. The outstanding functional group tolerance as well as an additive-based robustness screen[23] (Table 2; see the Supporting Information for details) clearly highlight the advantages of our methodology and the unmatched mildness of Cr organyls for carbonyl functionalizations.

Finally, insight into the mechanism was gained by performing various experiments (see the Supporting Information for details). Stern-Volmer luminescence quenching studies revealed that both starting materials and the product quench the excited state photocatalyst, but the quenching constant of the α-silyl amine substrate is around fifty times larger. These results would be consistent with a reductive quenching pathway of the photocatalyst by the α-silyl amine, similar to our previous studies and various other metalaphotoredox protocols.[12,13] The quantum yield of this protocol, however, was determined to be 12.5, inconsistent with a solely photoredox mechanism and implying a chain mechanism (Figure 3a).[24] Considering the redox potentials of the different species involved, a radical chain mechanism is unlikely, since the α-silyl amine **2** ($(E_{1/2}(\mathbf{2}^{\bullet+}/\mathbf{2})$ = 0.4 – 0.8 V vs SCE in MeCN)[14g,25a] would have to reduce a L_nCr^{III} species ($E_{1/2}(Cr^{III}/Cr^{II})$ = –0.51 V vs SCE in DMF)[25b], thermodynamically a highly unfavorable step (Figure 3b). The reaction should therefore primarily proceed according to another mechanism that is independent of redox-steps. One possible explanation involves σ-bond metathesis between a putative Cr-alkoxide **II** and either a TMS-amine adduct **III** or the α-silyl amine **2** (Figure 3c).[26] In the first case, the σ-bond metathesis would generate a Cr-amine species **IV**, which could regenerate the catalytically active α-aminoalkyl–Cr species **I** after loss of TMS^+. In the second case, the σ-bond metathesis would

generate the α-aminoalkyl–Cr species **I** directly. These mechanisms proceed exclusively *via* L_nCr^{III} intermediates and are consistent with the experimental data, but are speculative at this point. Further studies on the elucidation the mechanism of this aminoalkylation protocol are ongoing.

In conclusion, we have disclosed a mild and chemoselective silyl aminoalkylation of carbonyls for the synthesis of protected 1,2-amino alcohols. The reaction is enabled by a Cr/photoredox dual catalytic system, which allows the *in situ* generation of α-aminoalkyl-Cr reagents that react as carbanion equivalents. This methodology represents a catalytic and atom-economic alternative to traditional 1,2-amino alcohol preparations and enables a different retrosynthetic strategy, e.g. when the corresponding epoxides are not easily accessible. The reactions is chemoselective for aldehydes and can be used with complex structures in both coupling partners. The unique nature of our dual catalytic system was demonstrated by the functionalization of ketones and acyl silanes, classes of electrophiles that were previously shown not to react with alkyl–Cr^{III} reagents. More broadly, considering the ubiquity of amines, we believe further developments in the generation of α-amino carbanion equivalents will enable alternative syntheses of important building blocks and thus allow unusual retrosynthetic strategies.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website at DOI:10.1021/jacs.#######. Experimental and computational details (PDF)

CCDC Nr. 1960050 (**S8**, see Supporting Information) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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